UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/735,461	12/11/2003	Michael P. Czech	UMY-055	3119

959 7590 08/07/2007

LAHIVE & COCKFIELD, LLP
ONE POST OFFICE SQUARE
BOSTON, MA 02109-2127

EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	
MAIL DATE	**DELIVERY MODE**
08/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/735,461	**Applicant(s)** CZECH ET AL.	
	Examiner Richard Schnizer, Ph. D.	**Art Unit** 1635	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 25 July 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *25 July 2007*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *27,38-59,79 and 81-85*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☒ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Continuation of 5. Applicant's reply has overcome the following rejection(s): Rejection of claims 27, 38-59, 79, and 81-85 under 35 USC first paragraph.

Item 11, cont'd.

The request for reconsideration has been considered but does NOT place the application in condition for allowance.

Applicant's amendments overcame the rejection of claims 27, 38-59, 79, and 81-85 under 35 USC 112 first paragraph. This rejection is withdrawn.

Claims 27, 44-48, 50, 51, 56-59, 79, and 81-83 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Al-Hasani et al (J. Biol. Chem. 273(28): 17504-17510, 1998) in view of Clancy et al (US 20030087259).

Claims 38-43, 84, and 85 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Al-Hasani et al (J. Biol. Chem. 273(28): 17504-17510, 1998) and Clancy et al (US 20030087259) as applied to claims 27, 44-48, 50, 51, 56-59, 79, and 81-83 above, and further in view of Paquereau et al (Anal. Biochem. 204(1): 147-151, 1992).

Claim 49 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Al-Hasani et al (J. Biol. Chem. 273(28): 17504-17510, 1998) and Clancy et al (US 20030087259) as applied to claims 27, 44-48, 50, 51, 53-59, 79, and 81 above, and further in view of Standaert et al (J. Biol. Chem. 272(48): 30075-30082, 1997).

Claims 52-55 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Al-Hasani et al (J. Biol. Chem. 273(28): 17504-17510, 1998) and Clancy et al (US 20030087259) as applied to claims 27, 44-48, 50, 51, 53-59, 79, and 81 above, and further in view of McSwiggen et al (US Patent 7,022,828).

Applicant addresses the rejections at pages 11-21 of the response.

At page 12 Applicant argues that one of ordinary skill would not have found motivation to combine Al-Hasani with Clancy, and could not have done so with a reasonable expectation of success.

Applicant's arguments regarding motivation, set forth at page 13, are reiterated from the previous response received 12/12/06 and are unpersuasive for the reasons of record in the Final Rejection of 2/22/07. Specifically, MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In this case, Clancy taught that the activity of a polypeptide in a cell can be controlled by several alternative means including the use of negative mutants of the protein and the use of antisense or siRNA directed at the mRNA encoding the protein. See summary of invention paragraph 9, detailed description paragraph 234, and claim 21. Substituting one of these means for another is obvious, and requires no express suggestion in light of MPEP 2144.06. Accordingly, Applicant's argument that there is no motivation to select a specific member of the antagonists recited by Clancy is unpersuasive. Applicant also argues that one of ordinary skill would not have relied upon Clancy for any teaching because Clancy relates to diagnostic and therapeutic methods related to bone and cartilage formation, not glucose transport. This is unpersuasive because Clancy's general teaching that there exists a variety of alternative means to negatively control a polypeptide in a cell is not limited to the context of bone and cartilage formation and one

of ordinary skill in the art would clearly understand that it is applicable to polypeptides in general.

Applicant's arguments regarding a reasonable expectation of success are set forth at pages 14-16. Applicant's arguments at pages 15 and 16, which rely for support on the specification, Walters and Jelinek (2002), and Weil (2002) are reiterated from the previous response received 12/12/06 and are unpersuasive for the reasons of record in the Final Rejection of 2/22/07, reproduced below.

The specification at page 1, lines 23 and 24 indicates that no method has been reliably able to achieve specific ablation of gene or protein expression in adipocytes, and that adipocytes are difficult to work with and are not easily transfected with reagents that work in other cells such as fibroblasts. This is not supported by any reference and would appear to be incorrect in view of the example of Al Hasani, above, who taught electroporation of adipocytes to obtain specific ablation of protein expression. Further the prior art also taught transfection of adipocytes by electroporation, see e.g. Standaert et al (of record) at paragraph bridging pages 30075 and 30076, and paragraph bridging columns 1 and 2 on page 30079. As a result the teachings of the specification in this regard are not persuasive.

Walters taught that the effectiveness of siRNA may depend on transfection technique. Specifically, the results of Walters indicated that siRNAs delivered using cationic lipid transfection techniques were sequestered in the endosome/lysosome pathway in a nonadherent cell line, KAS-6/1 human myeloma cells. See page 417, column 1, first full paragraph. In order to circumvent this problem, Weil used

electroporation to deliver the siRNAs because it was known in the prior art that electroporation allowed direct delivery to the cytosol and did not depend on the endosome/lysosome (endocytic) pathway. This provides evidence that it was routine in the art at the time of the invention to optimize transfection protocols to determine which protocol worked best for a given cell line. It does not provide any evidence that one of ordinary skill in the art would not have had a reasonable expectation of success in obtaining RNAi in adipocytes by electroporating siRNAs. Accordingly, Applicant's reliance on Walters is misplaced.

The Weil reference is relied upon to teach that "the first difficulty in implementing RNA interference with a new cell type is optimizing the transfection process." However, this is essentially an admission that it is simply a matter of optimization, particularly in view of the fact that it was well known in the art that molecules could be electroporated into adipocytes (Al-Hasani, of record, and Zhang, above). Weil also suggested that electroporation of siRNAs can be efficient for nonadherent cells, and stated that the optimal parameters for the electroporation of siRNA differ from those of plasmids, allowing the use of milder conditions that induce less cell toxicity. See abstract. Weil does not provide any evidence that one of ordinary skill in the art would not have had a reasonable expectation of success in obtaining delivering siRNA to adipocytes by electroporation. Instead, Weil provides some motivation for selecting electroporation as a delivery technique for nonadherent cells, stating at page 1247, column 3, that for cells growing in suspension, calcium phosphate precipitation is inappropriate, and liposomes

and cationic lipids are unpredictable on new cell lines, whereas electroporation "can, a priori, be adapted to all cell types".

Taken together, the teachings of the specification, Walters, and Weil do not provide evidence that one of ordinary skill in the art would not have had a reasonable expectation of success in combining the cited references.

At page 14, Applicant argues that in order for siRNA to successfully silence a gene of interest, it is required that virtually all of the adipocytes take up functional siRNA. Applicant further argues that the successful electroporation of DNA into adipocytes is typically less than 10% efficient (relying for support on the instant specification at page 40, lines 15-17). The Examiner notes that Al-Hasani also reported about 10% efficiency (see e.g. page 17505, column 1, last sentence of first paragraph of RESULTS). Applicant concludes that one of ordinary skill would not have had a reasonable expectation of success. This argument is unpersuasive because Applicant's assertion that in order for siRNA to successfully silence a gene of interest, it is required that virtually all of the adipocytes take up functional siRNA is unsupported and illogical. The activity of siRNA in one cell has nothing to do with protein expression in another cell, such that if one cell takes up siRNA, one can reasonably expect to obtain inhibition of gene expression in that cell regardless of whether or not other cells in the culture were transfected. Applicant may have meant to argue that transfection of only 10% of the cells in a culture would be insufficient for the purposes of studying glucose transport. This would be unpersuasive because 10% efficiency proved to be sufficient for Al-Hasani. There is not reason of record to doubt that a similar transfection efficiency with

siRNA would be insufficient for the purpose of studying glucose transport in the system of Al-Hasani.

At page 15, Applicant presents evidence (Exhibits B-E) that allegedly support the non-obviousness of the present invention. Neither this evidence, nor the Declaration of Drs. Czech, Zhao, and Jiang, (Exhibit A), was considered because Applicant did not provide good and sufficient reasons why the evidence and Declaration were not presented before the final rejection.

Applicant's arguments regarding the rejections citing the Paquereau, Standaert, and McSwiggen references are reiterated from the previous response received 12/12/06 and are unpersuasive for the reasons of record in the Final Rejection of 2/22/07.

For these reasons the rejections are maintained.

Conclusion

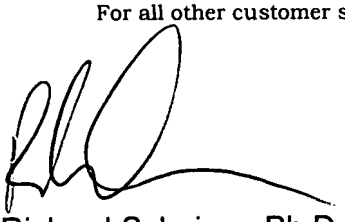
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.



Richard Schnizer, Ph.D.
Primary Examiner
Art Unit 1635